

Chelation of Toxic Metals: Current Interests

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Chelation therapy has long been regarded as a suitable approach to the therapeutic and even prophylactic removal of potentially toxic metals from body tissues. And there have been apparent successes in some areas, but there are also needs for a better understanding of the underlying pharmacology and for the development of safer and more effective agents.

There are currently three areas of interest in the clinical use of chelating drugs: treatment of heavy metal toxicity, removal of metals accumulated in body tissues because of genetic disorders, and chelation therapy of degenerative diseases of the blood vessels. An NIEHS symposium focused primarily on mechanisms, effectiveness, and potential adverse effects of traditional as well as new chelating agents (see Meeting Report in this issue). While most of the presentations concerned treatment of low-level lead exposures, the conference topics and discussions extended into the current status of chelation therapy for other disorders. There were also discussions of rationales for designing appropriate chelating agents. Experimental results of the laboratory testing of promising new drugs suggest that the development of more specific and effective agents is possible. None of the new drugs have been subjected to human clinical trials.

Much of the current interest in chelating agents stems from concerns about the possible beneficial effects of removal of toxic metals in people with low-level exposures without overt symptoms of toxicity. This interest is prompted by emerging evidence that toxic effects from exposures to lead, cadmium, and mercury may occur at levels previously thought to be harmless and at levels that do not produce overt clinical symptoms. It is now well established that low-level exposures to lead in early childhood may impair cognitive and behavioral development (1), while lifetime accumulations of cadmium in liver and kidney are associated with renal tubular dysfunction and hypercalciuria in later life (2). More recently, there have been assertions that mercury vapor released from dental amalgams might be responsible for a spectrum of chronic health problems (3,4). Although it may be debated as to what the lowest levels for concern might be for each of these metals, it is clear that the margin between the levels of exposure for persons living in the industrialized nations of the world and

levels of exposure currently recognized as producing the lowest adverse effect levels is small. While efforts to reduce exposure to these metals are being implemented, there are large populations of children and adults that might have exposures that exceed recommended levels or have some slight, though measurable, adverse effect.

In spite of the substantial decline in blood lead levels (BPb) for children in the United States over the last 10 years as determined by the most recent National Health and Nutrition Evaluation Survey, 35% of non-Hispanic, black children have BPb ≥ 10 $\mu\text{g}/\text{dl}$, in contrast to an overall average of about 4% (5). It may be argued that the best treatment for the overexposed children is removal from potential sources of exposure, but it is unlikely that the major risk factors, homes containing lead-based paint, can be corrected in the near future. From this perspective chelation becomes an appealing alternative. However, there are a number of unanswered questions regarding the effectiveness of available chelating agents. There is currently no conclusive evidence that reduction of blood lead levels by chelation will reverse neurological effects already present. Also, historically, the drug of choice for treatment of lead poisoning is CaNa_2EDTA , which is administered by infusion, is relatively nonspecific and promotes loss of essential cations. Therefore, the use of EDTA has been reserved for instances of clinical lead toxicity. However, with the recent availability of DMSA (succimer), an orally administered drug, the enthusiasm for therapy of children with low-level exposure to lead is growing (6). But this alternative drug only has FDA approval for reduction of BPb levels >45 $\mu\text{g}/\text{dl}$.

The adverse effects of excess cadmium exposure become evident in older adult populations: renal tubular dysfunction and hypercalciuria, which is a factor in the development of osteoporosis (7). Daily intake of cadmium from food in most industrialized countries is about 10–50 $\mu\text{g}/\text{day}$; the upper limit recommended by the U.S. EPA Integrated Risk Information System is 70 $\mu\text{g}/\text{day}$, similar to the permissible weekly intake recommendation of the Joint Food and Agriculture Organization/World Health Organization Expert Committee (8). Renal tubular dysfunction attributable to excess cadmium exposure

affects large populations of adults in Japan, The Netherlands, and Belgium (2,9). Because of the long retention time in soft-tissue (half-life of 30 years), the renal effects are not reversible within 10 or 15 years or longer, and may be progressive. It seems appropriate therefore to look to a chelating agent to reduce the problem, at least in severe cases, but none is available at present.

Concern about mercury exposure is largely from consumption of fish containing methylmercury, which may be a hazard to the developing fetus. The EPA and FDA have monitored fish consumption and exposures to high-risk populations in the United States. Again, there is only a small margin of safety for large groups of children, and, as discussed at the conference, methylmercury is probably not chelatable. A second exposure to mercury for persons in the general population is elemental mercury or mercury vapor from dental amalgams. Although mercury-containing amalgams have been used in dentistry for more than 100 years without demonstrated adverse effects, it has now been shown that mercury in tissues can be related to the number of mercury-containing dental fillings and that there is a relationship between numbers of mercury amalgams and mercury content of tissues, including the nervous system, of newborn infants (10). The chelating agents DMSA and DMPS can enhance urinary excretion of elemental mercury, which, in turn, can be related to the number of mercury-containing dental fillings. While there is no substantiated health effect from tissue levels of mercury attributable to dental amalgams, it is alleged that a number of nonspecific, chronic conditions can be ameliorated by removal of the amalgams or by chelation. None of this has been supported by confirmed peer-reviewed research, but it has attracted the public interest in removal of amalgam fillings and chelation therapy for removal of mercury.

Chelation therapy has long been the only method for reducing body burdens of metals resulting from genetic disorders of metal metabolism such as copper accumulation in Wilson's disease, cystine crystal formation in cystinuria, and removal of tissue iron in hemochromatosis. For these disor-

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ders the rationale for chelation therapy is supported to some degree by clinical experience and there are, at present, no alternatives. However, there is an expanding interest in chelation therapy for the treatment of degenerative vascular disease due to arteriosclerosis. The initial assumption was that chelation with EDTA worked by chelating calcium from atherosclerotic plaques and hence improved blood flow in narrowed vessels. While this hypothesis has lost favor, practitioners of chelation therapy believe that EDTA works by chelating iron and copper, reducing the generation of free radicals and subsequent lipid peroxidation (11,12). Literature aimed at the lay reader and widely available in health food stores favors chelation therapy for treatment of "narrowing of the arteries" rather than established techniques of angioplasty and bypass surgery (13,14). The effectiveness of chelation therapy for treatment of peripheral vascular disease is being debated (15); double-blind, randomized studies do not support clinical efficacy (16,17). On the other hand, one might see the appeal of the relatively low cost, noninvasive nature of this approach. Lay literature provides considerable anecdotal support for effectiveness and even endorsements by some physicians.

All of these interests and needs argue for increased research efforts to provide a better understanding of what chelation therapy does and does not do and to identify its risks. In most cases it is not difficult to demonstrate increased excretion of the metal, but in few instances has the clinical efficacy of the treatment been demonstrated with any scientific rigor (18). Although there may be evidence for the ability of a particular agent to enhance excretion of a metal in question, there is a paucity of evidence that any of the uses of chelation therapy reverses toxicity at the cellular level or prevents progression of the pathology

produced by the accumulated metal.

It is apparent that there are serious deficiencies in the understanding and effectiveness of chelating agents for the removal of toxic metals and treatment of metal toxicities. There are many reasons for this state of the science. There has not been sufficient basic research to elucidate the cell effects and mechanisms of action and effects of chelating agents on the biokinetics of toxic metals. Investment in research in these topics has lagged because of the view that need for chelation therapy is secondary to reduction in exposure. Another major reason is the large costs associated with drug development for a small and specialized market. The clinical testing of a chelating agent involves identification of an appropriate cohort, a random double-blind design that incorporates scientifically credible measures of clinical outcome, and a large financial outlay. Added to these difficulties is ethical acceptance of the use of placebos essential for the conduct of a double-blind study. These considerations do not foster confidence that the scientifically desired ideal for these therapies will be imminent. However, awareness of the deficiencies of knowledge should be reason for caution not to do harm and not to generate false expectations.

REFERENCES

1. CDC. Preventing lead poisoning in young children: a statement by the Centers for Disease Control. Atlanta, GA: Centers for Disease Control, 1991.
2. WHO. Cadmium. IPCS environmental health criteria 134. Geneva: World Health Organization, 1992.
3. Skare I, Engqvist A. Human exposure to mercury and silver released from dental amalgam restorations. *Arch Environ Health* 49:384-394 (1994).
4. Basu MK, Wilson HJ, Krishnan G. Mercury risk from teeth. *Nature* 349:109 (1991).

5. Pirkle JL, Brody DJ, Gunter EW, Kramer RA, Paschal DC, Flegal KM, Matte TD. The decline in blood lead levels in the United States. *J Am Med Assoc* 272:284-291 (1994).
6. Mortensen ME. Succimer chelation: what is known. *J Pediatr* 125:233-234 (1994).
7. Goyer RA, Epstein S, Bhattacharyya M, Korach KS, Pounds J. Environmental risk factors for osteoporosis. *Environ Health Perspect* 102:390-394 (1994).
8. WHO. Forty-first report of the Joint FAO/WHO Expert Committee on Food Additives. WHO technical report series 837. Geneva: World Health Organization, 1993; 28-30.
9. Buchet JP, Lauwerys R, Roels H, et al. Renal effects of cadmium body burden of the general population. *Lancet* 336:699-702 (1990).
10. Drasch G, Schupp I, Hoff H, Reinke R, Roeder G. Mercury burden of human fetal and infant tissues. *Eur J Pediatr* 153:607-610 (1994).
11. Babu AN, Gomez-Penna H. Iron chelating agents are not useful in treating atherosclerosis. *Ann Int Med* 121:384-385 (1994).
12. Voest EE, Vreugdenhil G, Marx JJ. Iron-chelating agents in non-iron overload conditions. *Ann Int Med* 120:490-499 (1994).
13. Walker M. The chelation way. Garden City, NY: Avery Publishing Group, 1990.
14. Brecher H, Brecher A. Forty something forever: a consumer's guide to chelation therapy. Herndon, VA: Health Savers Press, 1992.
15. Chappell LT, Miranda R, Hancke C, Frackelton JP, Carter JP. EDTA chelation treatment for peripheral vascular disease. *Ann Int Med* 231:429-430 (1992).
16. Guldager B, Jørgensen SJ, Nielsen JS, Klærke A, Mogensen K, Larsen KE, Reimer E, Holm J, Øttesen S. EDTA treatment of intermittent claudication—a double blind placebo-controlled study. *J Int Med* 231:261-267 (1992).
17. van Rij AM, Solomon C, Packer SGK, Hopkins WG. Chelation therapy for intermittent claudication: a double blind, randomized, controlled trial. *Circulation* 90:1194-1199 (1994).
18. Kosnett MJ. Unanswered questions in metal chelation. *Clin Toxicol* 30:529-547 (1992).

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